# Impact of 123 I-MIBG scintigraphy on clinical decision making in pheochromocytoma and paraganglioma

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Abstract: CONTEXT Cross sectional imaging with computed tomography (CT) or magnetic resonance imaging (MRI) is regarded as a first-choice modality for tumor localization in patients with pheochromocytoma and paraganglioma (PPGL). 123I-labeled metaiodobenzylguanidine (123I-MIBG) is widely used for functional imaging but the added diagnostic value is controversial. OBJECTIVE To establish the virtual impact of adding 123I-MIBG scintigraphy to CT or MRI on diagnosis and treatment of PPGL. DESIGN International multicenter retrospective study. INTERVENTION None. PATIENTS 236 unilateral adrenal, 18 bilateral adrenal, 48 unifocal extra-adrenal, 12 multifocal and 26 metastatic PPGL. MAIN OUTCOME MEASURES Patients underwent both anatomical imaging (CT and/or MRI) and 123I-MIBG scintigraphy. Local imaging reports were analyzed centrally by two independent observers who were blinded to the diagnosis. Imaging-based diagnoses determined by CT/MRI only, 123I-MIBG only, and CT/MRI combined with 123I-MIBG scintigraphy were compared with the correct diagnoses. RESULTS The rates of correct imaging-based diagnoses determined by CT/MRI only versus CT/MRI plus 123I-MIBG scintigraphy were similar: 89.4 versus 88.8%, respectively, (P=0.50). Adding 123I-MIBG scintigraphy to CT/MRI resulted in a correct change in the imaging-based diagnosis and ensuing virtual treatment in four cases (1.2%: two metastatic instead of non-metastatic, one multifocal instead of single, one unilateral instead of bilateral adrenal) at the cost of an incorrect change in seven cases (2.1%: four metastatic instead of non-metastatic, two multifocal instead of unifocal and one bilateral instead of unilateral adrenal). CONCLUSIONS For the initial localization of PPGL, the addition of 123I-MIBG scintigraphy to CT/MRI rarely improves the diagnostic accuracy at the cost of incorrect interpretation in others, even when 123I-MIBG scintigraphy is restricted to patients who are at risk for metastatic disease. In this setting, the impact of 123I-MIBG scintigraphy on clinical decision-making appears very limited.

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# Impact of [123] I-MIBG scintigraphy on clinical decision making in pheochromocytoma and paraganglioma

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***Context:*** Cross sectional imaging with computed tomography (CT) or magnetic resonance imaging (MRI) is regarded as a first-choice modality for tumor localization in patients with pheochromocytoma and paraganglioma (PPGL). [123]I-labeled metaiodobenzylguanidine ([123]I-MIBG) is widely used for functional imaging but the added diagnostic value is controversial.
***Objective***: To establish the virtual impact of adding [123]I-MIBG scintigraphy to CT or MRI on diagnosis and treatment of PPGL.
***Design:*** International multicenter retrospective study.
Intervention: None.
***Patients:*** 236 unilateral adrenal, 18 bilateral adrenal, 48 unifocal extra-adrenal, 12 multifocal and 26 metastatic PPGL.
***Main Outcome Measures:*** Patients underwent both anatomical imaging (CT and/or MRI) and [123]I-MIBG scintigraphy. Local imaging reports were analyzed centrally by two independent observers who were blinded to the diagnosis. Imaging-based diagnoses

determined by CT/MRI only, $^{123}$I-MIBG only, and CT/MRI combined with $^{123}$I-MIBG scintigraphy were compared with the correct diagnoses.

***Results**:* The rates of correct imaging-based diagnoses determined by CT/MRI only versus CT/MRI plus $^{123}$I-MIBG scintigraphy were similar: 89.4 versus 88.8%, respectively, (*P*=0.50). Adding $^{123}$I-MIBG scintigraphy to CT/MRI resulted in a correct change in the imaging-based diagnosis and ensuing virtual treatment in four cases (1.2%: two metastatic instead of non-metastatic, one multifocal instead of single, one unilateral instead of bilateral adrenal) at the cost of an incorrect change in seven cases (2.1%: four metastatic instead of non-metastatic, two multifocal instead of unifocal and one bilateral instead of unilateral adrenal).

***Conclusions**:* For the initial localization of PPGL, the addition of $^{123}$I-MIBG scintigraphy to CT/MRI rarely improves the diagnostic accuracy at the cost of incorrect interpretation in others, even when $^{123}$I-MIBG scintigraphy is restricted to patients who are at risk for metastatic disease. In this setting, the impact of $^{123}$I-MIBG scintigraphy on clinical decision-making appears very limited.

In this large retrospective study, we show that the impact of 123I-MIBG scintigraphy on clinical decision-making in patients with pheochromocytoma and paraganglioma appears very limited. .

## INTRODUCTION

$^{123}$I-metaiodobenzylguanidine ($^{123}$I-MIBG) scintigraphy is commonly used for functional imaging of pheochromocytomas and paragangliomas (PPGLs), tumors arising from respective adrenomedullary and extra-adrenal chromaffin cells. Such tumors are highly hereditable since up to 40% harbor a known germline mutation in one of the tumor susceptibility genes [1,2]. Patients with hereditary PPGLs tend to develop tumors at a younger age and are more likely to have bilateral, multifocal, unifocal extra-adrenal and/or malignant disease [3].

Imaging studies are essential in the diagnostic work-up of patients with PPGLs for tumor localization and staging and thus for guiding the optimal treatment. Computed tomography (CT) is the main imaging modality because of its high diagnostic sensitivity of more than 90% for adrenal PPGL, while lower for extra-adrenal, recurrent or metastatic PPGLs [4,5]. Specificity is limited but can be improved substantially when unenhanced attenuation is considered [5,6].

Improved specificity can be achieved using functional imaging modalities that target specific cell membrane and vesicular catecholamine transport systems as well as cell membrane receptors. $^{123}$I-MIBG is widely available and the most often used radioligand for PPGLs, yielding a specificity of 70-100% for adrenal PPGL and 84-100% for extra-adrenal PPGL [7-10]. Nevertheless, $^{123}$I-MIBG scintigraphy may provide false-positive test results in about 10% of the patients, especially due to physiological tracer uptake by normal adrenals [11,12].

Although sensitivity of $^{123}$I-MIBG scintigraphy (between 84 and 100%) is lower than that of CT, it is considered helpful for confirming or excluding multifocal or metastatic disease. Sensitivity appears to be particularly low in patients with *SDHx* mutations (<50%), in patients with metastatic disease (56-83%), and in those with extra-adrenal tumor localization (56-75%) as shown in several small studies [8,13-16]. The Endocrine Society guideline suggests limiting the use of $^{123}$I-MIBG scintigraphy to patients at risk for or with proven metastatic disease to help identify patients who may benefit from treatment with therapeutic doses of $^{131}$I-MIBG. Risk factors for metastatic disease are large tumor size (> 6 centimeter), extra-adrenal or multifocal tumor locations, as well as hereditary and/or recurrent disease [4].

Despite its extensive use, the scientific basis of these $^{123}$I-MIBG scintigraphy recommendations and its actual clinical benefits in all patients with a PPGL is a matter of

debate [16]. To date, few studies provide evidence for the additional value of $^{123}$I-MIBG scintigraphy to CT/MRI as part of the routine diagnostic evaluation of patients with PPGL when it comes to therapeutic planning and patient outcomes. A recent systematic review failed to demonstrate a substantial clinical benefit of functional imaging in patients with PPGLs over CT/MRI only [17]. It is thus quite conceivable that $^{123}$I-MIBG scintigraphy could be omitted in a subset of patients who could proceed to surgery without preoperative $^{123}$I-MIBG scintigraphy, especially in patients with a biochemically established PPGL in whom CT/MRI has identified a small (eg, <6 cm) adrenal tumor [18,19]. The aim of this retrospective study was to evaluate the added value of $^{123}$I-MIBG scintigraphy on top of CT/MRI as compared to only CT/MRI for the diagnosis and consequent treatment of PPGLs.

## METHODS

### Patient Population

This retrospective study included 392 patients with a confirmed PPGL who underwent preoperative diagnostic CT and/or MRI scanning as well as $^{123}$I-MIBG scintigraphy between January 1985 and March 2016. Patients were included at seven centers taking part in the European Network for the Study of Adrenal Tumors (ENS@T) including one US center, the Mayo Clinic. Patients were evaluated for PPGL because of clinical suspicion of PPGL based on symptoms and signs, an adrenal incidentaloma, recurrent PPGL or as part of case detection testing for hereditary PPGL. In total, 52 patients were excluded due to several factors: age <18 years (n=14), known presence of another malignancy (n=4), unavailable biochemical test results (n=10), unavailable pathology results (n=3), presence of skull base and neck paraganglioma only (n=10), incomplete imaging reports (n=9) or unreliable imaging results due to technical failures (n=2). In cases of recurrent disease, only the first disease episode for which clinical data and imaging reports were available was included in the analysis.

Finally, 340 patients from the following centers were included for analysis: Radboud University Medical Centre Nijmegen, the Netherlands (n=166); Mayo Clinic Rochester, USA (n=90); University Hospital Würzburg, Germany (n=28); University Hospital Munich, Germany (n=19); Institute of Cardiology Warsaw, Poland (n=16); University Hospital Carl Gustav Carus Dresden, Germany (n=12); Careggi University Hospital Florence, Italy (n=9).

The following data were collected: age at presentation, sex, biochemical test results (plasma free and/or 24 hour urine fractionated metanephrines and/or catecholamines), genotype, pathology reports including maximum tumor diameter, the correct diagnoses, as well as imaging reports of CT/MRI and $^{123}$I-MIBG scintigraphy.

The presence of germline mutations and large deletions was investigated for the following genes in 218 patients (64%): succinate dehydrogenase (SDH) complex subunits and cofactor 2 (*SDHA/B/C/D/AF2*), rearranged during transfection *(RET),* von Hippel-Lindau (*VHL*), neurofibromatosis type 1 (*NF1*), transmembrane protein 127 (*TMEM127),* and myc-associated factor X (*MAX*). In 82 patients, a pathogenic germline mutation was established (19 *SDHB,* 14 *SDHD*, 9 *VHL*, 32 *RET*, 3 *TMEM*127, 3 *MAX*, 2 *SDHA*). Twenty patients had a clinical diagnosis of NF1, resulting in a total proportion of hereditary PPGL of 47%.

Patients provided informed consent to collect clinical data, in accordance with institutional ethics–approved protocols for each center. At the Radboud University Medical Centre data were collected under conditions of regular clinical care with ethics committee approval for the use of those data for scientific purposes.

### Biochemical testing

All patients underwent biochemical testing before and after surgery. Biochemical testing was performed in accordance with local protocols and by local assays, applying the locally used

reference values. The biochemical phenotype was determined on the basis of plasma free metanephrines related to the upper limits of normal. If plasma free metanephrines were not available, urinary metanephrines, urinary catecholamines or plasma catecholamines were utilized, in order of preference. Biochemical phenotypes were categorized in those patients in whom plasma metanephrines were available as described by Eisenhofer et al. [20]. Adrenergic and dopaminergic phenotypes were classified by respective increases of plasma metanephrine and methoxytyramine above the upper reference intervals and associated increments, relative to the sum of increments of all three metabolites, of larger than 5% for metanephrine and 10% for methoxytyramine. Noradrenergic tumors were defined as those with predominant increases of only normetanephrine, accompanied by either normal plasma concentrations of metanephrine and methoxytyramine (below the upper reference intervals) or by increases of less than 5% for metanephrine and 10% for methoxytyramine relative to the sum of increments for all three metabolites.

**Imaging**

All imaging studies were performed preoperatively according to local protocols. Of the 340 included patients, 257 were evaluated by CT, 53 by MRI, and 30 by both CT and MRI. Of 287 patients who underwent CT scanning, only post-contrast images (n=160) or delayed contrast washout CT (n=87) were performed. In forty cases, no contrast agent was administered. The body areas scanned by CT comprised the abdomen only in 218 patients (with 46 patients also including the pelvis); thorax only (always including the adrenals) in 8 patients; both thorax and abdomen in 49 patients (7 patients including the pelvis); and combination of cerebrum, neck, thorax, abdomen, and pelvis in 3 patients. In 9 patients the window of CT imaging was unknown but at least comprising the adrenals.

The window of MRI scanning comprised the abdomen only in 51 patients; thorax only in 4 patients; cardiac only in 1 patient; spine in 4 patients; both thorax and abdomen in 3 patients; both abdomen and pelvis in 14 patients. In 6 patients the window of MRI imaging was unknown but at least comprising the adrenals.

All patients underwent $^{123}$I-MIBG scintigraphy. 179 were evaluated by $^{123}$I-MIBG SPECT and 101 by $^{123}$I-MIBG SPECT/CT. In 60 patients, only planar $^{123}$I-MIBG images were obtained. Regarding the sequence of imaging, a minority of 26 patients (7.6%) underwent $^{123}$I-MIBG scintigraphy as an initial scan prior to CT/MRI imaging.

**Data analysis**

The correct diagnosis of unilateral adrenal, bilateral adrenal, unifocal extra-adrenal, multi-focal or metastatic PPGL was defined by the local investigator/clinicians using all available data on histology, imaging and follow-up. This correct diagnosis was considered as the reference standard to evaluate the numbers of correct and incorrect imaging-based diagnoses.

Evaluation of the locally generated imaging reports was performed centrally by two independent investigators (DR and IP) who were blinded to the correct diagnosis and the final treatment. If needed, reports were translated into English by the local co-investigators. Images were not re-reviewed. Lesions described as PPGL or as ‘indeterminate’ tumor lesions were included in the analysis. Adrenal lesions on CT and/or MRI that were described as (possible) adenoma were still classified as PPGL when no other tumors were present because all patients had PPGL per inclusion. Adrenal glands with 123I-MIBG uptake described as definite or possibly pathological were classified as PPGL, unless the adrenal glands were completely normal on CT/MRI. Any lesions on CT and/or MRI or 123I-MIBG scintigraphy described as possible metastases were classified as metastases. The latter could not be overruled for the imaging-based diagnosis by any other imaging technique. Finally, the results from both investigators were compared and in case of discrepancies, these were re-analyzed to reach consensus, if necessary involving additional observers (HT and JL).

Imaging-based interpretations of diagnoses and ensuing virtual treatments were determined retrospectively on the basis of imaging results according to three scenarios (Figure 1): 1) CT/MRI only; 2) 123I-MIBG scintigraphy only; and, 3) combined results of CT/MRI and 123I-MIBG scintigraphy. Diagnoses were classified according to the following categories: 1) no PPGL if no tumor was observed; 2) unilateral PPGL if one tumor was located in one adrenal gland; 3) unifocal extra-adrenal PPGL if one tumor was located outside the adrenal glands; 4) bilateral PPGL if tumors were seen in both adrenal glands and nowhere else; 5) multi-focal PPGL if two or more tumors were found (except if these were restricted to both adrenals); and, 6) metastatic PPGL if lymph node or distant metastases were found (irrespective of the primary tumor). The virtual ensuing therapeutic modalities (Figure 1) were classified as follows: 1) unilateral adrenalectomy; 2) unifocal extra-adrenal tumor resection; 3) bilateral adrenalectomy; 4) multi-focal resection; and, 5) treatment of metastatic disease, respectively.

Rates of correct imaging-based diagnoses according to the three imaging scenarios were compared mutually. Correct and incorrect changes to imaging-based diagnoses by inclusion of 123I-MIBG scintigraphy to CT/MRI results (scenario 3) were registered. This was also done for subsequent virtual treatment. A subgroup analysis was performed in patients at risk for metastatic disease, as for these patients the use of 123I-MIBG scintigraphy is specifically recommended by the Endocrine Society Clinical Practice guideline (3).

### Statistical Analysis

The level of inter-observer discrepancy was assessed using Cohen's kappa. The McNemar test was used to test for the difference in proportion of concordant diagnoses based on CT/MRI only diagnoses, $^{123}$I- MIBG scintigraphy only diagnoses and CT/MRI combined with $^{123}$I-MIBG scintigraphy diagnoses as compared to the correct diagnoses. McNemar test was also used to test the impact of changes in diagnosis after addition of $^{123}$I-MIBG scintigraphy to CT/MRI only. A two-sided $P < 0.05$ was considered significant. Statistical analysis was performed using Statistical Package for the Social Sciences (SPSS for Windows 12; SPSS Inc., Chicago, IL).

## RESULTS

The study group consisted of 340 patients, including 314 (92.4%) with a diagnosis of non-metastatic PPGL and 26 (7.6%) with metastatic PPGL and variable biochemical phenotypes and other presentations (Table 1).

### Imaging-based diagnoses

Inter-observer agreement regarding the diagnoses based on different imaging scenarios was reached in 322 cases (kappa 0.90) and 8 after re-analysis. For 10 additional cases the final decision was made after discussion with the additional observers.

The majority (69.4%) of the patients had a correct diagnosis of unilateral adrenal PPGL (Table 2).The imaging-based diagnoses were similarly distributed across different scenarios. However, 123I-MIBG scintigraphy by itself failed to localize any tumor in 26 patients with a correct diagnosis of PPGL (7.7%).

### Diagnostic accuracy

Overall, the concordance with the correct diagnoses was similar for all three scenarios: CT/MRI only 89.4%, $^{123}$I-MIBG only 87.1% and CT/MRI plus $^{123}$I-MIBG 88.8%. These rates were not significantly different (Table 3). The rate of discrepancy in diagnosis was independent of the biochemical phenotype (data not shown).

In patients with non-metastatic PPGL, the CT/MRI-based diagnosis was incorrect in 31 cases (8.9 %), 23 of which were misclassified as metastatic disease instead of the correct diagnoses of 14 unilateral adrenal, 3 bilateral adrenal and 6 unifocal extra-adrenal disease.

When including $^{123}$I-MIBG scintigraphy on top of CT/MRI, the imaging-based diagnosis was incorrect in 35 cases (11.1%), 27 of which were misclassified as metastatic, 4 as bilateral instead of unilateral, 4 as multi-focal instead of unifocal disease.

In the patients with metastatic disease, this CT/MRI-based diagnosis was missed in 5 cases (19.2%) and in 3 cases (11.5%) with additional inclusion of $^{123}$I-MIBG.

**Impact of $^{123}$I-MIBG scintigraphy on imaging-based diagnosis and ensuing management**

Overall, inclusion $^{123}$I-MIBG scintigraphy to CT/MRI resulted in a correct change in the imaging-based diagnosis in four cases (1.2%): (two metastatic instead of non-metastatic, one multifocal instead of single, one unilateral instead of bilateral adrenal) at the cost of an incorrect change in seven cases (2.1%): (four metastatic instead of non-metastatic, two multifocal instead of single and one bilateral instead of unilateral adrenal) (Table 4). Regarding the four patients with false positive findings on imaging suggesting metastases, the duration of follow-up was 1, 3, 3 and 6 years, respectively. During this follow-up, these patients lacked (malignant) recurrence.

Details on the impact of adding $^{123}$I-MIBG scintigraphy to CT/MRI on the virtual management of individual patients are provided in Table 5. Overall, by taking $^{123}$I-MIBG into account, one incomplete surgery was prevented. This was due to the fact that a chest lesion would have been missed because the CT scan in this patient only included the abdominal region. On the other hand, as compared to CT/MRI only, $^{123}$I-MIBG would also result in one extra redundant surgery and the unjustified omission of four surgeries (3 unilateral adrenal PPGL and 1 unifocal extra-adrenal PPGL).

Patients in whom the initial CT/MRI scan had been limited to the abdomen and in whom $^{123}$I-MIBG scintigraphy prompted additional anatomical imaging of the chest and/or pelvis were specifically analyzed in order to correct for a potential bias towards a favorable outcome of CT/MRI when taking into account all anatomical data. This sequence of imaging, *i.e.* CT/MRI followed by $^{123}$I-MIBG scintigraphy followed by additional CT/MRI, was observed in three patients. In two patients, this did not confirm the presence of additional PPGLs and the lesions on $^{123}$I-MIBG scintigraphy were considered false-positive. In one patient, however, a chest lesion on $^{123}$I-MIBG scintigraphy prompted additional anatomical imaging, leading to the diagnosis of a cardiac PPGL, that for obvious reasons initially had been missed on abdominal CT.

If $^{123}$I-MIBG scintigraphy would have been limited to a subgroup of patients at risk for metastases as recommended by the Endocrine Society Clinical Practice guideline (3), $^{123}$I-MIBG scintigraphy would have been performed in a subgroup of 163 patients (47.9%), including 32 with a previous history of PPGL, 56 with unifocal extra-adrenal or multi-focal location and 75 with a tumor size > 6 centimeter. Adding $^{123}$I-MIBG scintigraphy to CT/MRI resulted in a correct change in the imaging-based diagnosis in 3 patients: two metastatic instead of unifocal, one multi-focal instead of unifocal disease. This was at the cost, however, of incorrect changes in the imaging-based diagnosis in 3 other patients: one metastatic instead of unilateral adrenal, and two multi-focal instead of unifocal disease.

## DISCUSSION

In this large retrospective study, we investigated the potential impact of $^{123}$I-MIBG scintigraphy as an add-on to CT/MRI as part of the pre-operative workup in patients with PPGL. Addition of $^{123}$I-MIBG scintigraphy to CT/MRI changed the diagnosis correctly in 1.2% of the patients, whereas it changed the diagnosis incorrectly in 2.1% of the patients. Even in patients at risk for metastatic disease there appeared to be no benefit of adding $^{123}$I-MIBG scintigraphy to CT/MRI. Addition of $^{123}$I-MIBG scintigraphy did not decrease the number of potential incorrect therapeutic decisions. Our results indicate that the application

of $^{123}$I-MIBG scintigraphy in the initial evaluation of PPGL has limited benefit and may even lead to inappropriate clinical management decisions.

CT/MRI has a crucial role in the pre-operative evaluation of patients with biochemically established PPGL. However, anatomical imaging offers suboptimal specificity, yielding false-positive results in a number of patients. On the other hand, lesions may be missed because of an unusual location or the presence of surgical clips [16]. Indeed, our study confirms that CT/MRI is not optimal, since in 10% of patients the diagnosis based on CT/MRI was incorrect, mainly due to detection of lesions that were not PPGLs. Functional imaging could be of complementary utility given its high specificity. Moreover, whole body evaluation may detect additional PPGL lesions. $^{123}$I-MIBG scintigraphy is the most widely available and used functional imaging modality. Despite these potential benefits, studies on the actual impact of $^{123}$I-MIBG scintigraphy for the diagnosis and therapeutic consequence in clinical practice are limited in these tumors [17,21].

Our results do not support the indiscriminate routine use of $^{123}$I-MIBG scintigraphy in addition to anatomical imaging in the routine work-up of all patients with a PPGL as it appears to lead to both incorrect and correct changes in the diagnosis and treatment. This is in line with the contention that $^{123}$I-MIBG scintigraphy is not considered beneficial in patients with small adrenergic unilateral adrenal tumors without known mutations as it is extremely unlikely that in these cases the PPGL is multi-focal or metastatic [22]. Indeed, the results of the present study support this contention. The benefit in a limited number of patients and a negative impact in another subset, suggests the need for restricting $^{123}$I-MIBG scintigraphy imaging to sub-groups that may benefit the most. One specific category of patients is those with an increased risk for multifocal or metastatic disease. In the Endocrine Society clinical practice guideline (3), it was recommended to limit use of $^{123}$I-MIBG scintigraphy to specific patient groups: 1) established metastatic disease for evaluating the eligibility for $^{131}$I-MIBG treatment; and, 2) an increased risk of metastases due to unifocal extra-adrenal or multifocal tumor location, recurrent disease, large tumors (>6 cm) or a germline mutation. Our subgroup analysis of such 'high risk' patients showed that $^{123}$I-MIBG scintigraphy would have a positive impact on the diagnosis in 3/163 patients (<2%) at the cost of a negative impact in just as many patients, the latter resulting in inappropriate therapeutic decision making.

Based on our findings, it could be suggested that $^{123}$I-MIBG scintigraphy should only be used in patients with metastatic PPGL who might benefit from $^{131}$I-MIBG radiotherapy. It should be noted, however, that $^{123}$I-MIBG scintigraphy may remain useful in selected cases. Such cases include those where it is necessary to distinguish a local recurrence from post-surgical anatomical changes/surgical clips, patients with contraindications for CT/MRI (e.g. allergy to intravenous contrast, metallic devices/pacemaker, claustrophobia) and in patients with equivocal findings on anatomical imaging such as apparently compound adrenal tumors or asymmetrical bilateral adrenal tumors. In addition, when CT/MRI is limited to the abdomen or even the adrenal area, $^{123}$I-MIBG scintigraphy could potentially identify additional lesions. In the present study, this was the case for a single patient only, however.

An often promulgated potential advantage of $^{123}$I-MIBG scintigraphy is the ability to detect additional lesions missed on CT (or MRI), even though the sensitivity of $^{123}$I-MIBG scintigraphy is limited, particularly for metastases [23-25]. When relying on $^{123}$I-MIBG scintigraphy alone, the diagnosis would be correct in 88.9% and 65.4% of the patients with non-metastatic and metastatic PPGL, respectively. Compared to CT/MRI alone, $^{123}$I-MIBG correctly revealed additional lesions in less than 1% of the patients. When $^{123}$I-MIBG scintigraphy was added to CT/MRI, two additional cases of metastatic disease were discovered.

Despite its claimed specificity, $^{123}$I-MIBG scintigraphy yielded several false-positive lesions, potentially leading to an incorrect diagnosis and treatment in those patients. In one

patient this was attributable to $^{123}$I-MIBG uptake by an adrenal gland with an adenoma based on MRI, which was mistaken for a PPGL. In addition to adrenal lesions, erroneous metastatic lesions and extra-adrenal lesions (based on normalized post-operative biochemical results) were detected in two and four patients, respectively. This drawback of $^{123}$I-MIBG scintigraphy was also observed by Mihai et al, who reported false-positive lesions in a proportion as high as 23% of all patients due to adrenocortical adenomas, non-adrenal pathology, and tracer uptake adjacent to the adrenal [18].

This study has several limitations that should be acknowledged. First, it involved a retrospective analysis of the theoretical results of different imaging scenarios. Data were collected retrospectively from several international centers with slightly different local practices for the biochemical diagnosis and localization of PPGLs. Second, in some participating centers alternative or additional functional imaging modalities such as positron emission tomography (PET) scans might have been performed, affecting the diagnosis of reference. This may have led to selection bias when evaluating only those patients who underwent $^{123}$I-MIBG scintigraphy. The diagnostic performance of other functional imaging modalities used in some centers to diagnose PPGL, such as $^{18}$F-FDOPA PET, $^{18}$F-FDG PET and $^{68}$GA-DOTA-peptides PET, was beyond the scope of this study. In particular, based on recent findings, it is expected that for the assessment of the extent of the disease, 68GA-DOTA-peptides PET will become the functional imaging of choice[26,27]. Third, our analysis fully relied on imaging reports that were generated by local radiologists and nuclear medicine physicians from the different centers. Furthermore, there were differences in scanners and scanning protocols used. The body regions evaluated by CT/MRI were not uniform and often limited to the abdomen. Also the sequence of imaging was not controlled for. The vast majority of patients, however, underwent CT/MRI prior to $^{123}$I-MIBG scintigraphy. When taking to account all imaging data, including the results of additional CT/MRI prompted by $^{123}$I-MIBG scintigraphy, this could lead to a bias in favor of anatomical imaging. Nevertheless, we showed that the impact of sequence was in fact minimal. Finally, in the analysis, we set a low threshold for classifying any lesion of unknown significance as PPGL lesion, potentially increasing the false positive rates and decreasing the false-negative rates, although these were similar to previous reports [18]. It might be that in reality additional imaging was performed to characterize lesions of uncertain significance that were not taken into account in our analysis.

In conclusion, the results of this retrospective study suggest that the benefits of the addition of $^{123}$I-MIBG scintigraphy to CT/MRI for localization of PPGL are limited. The advantages in some patients do not clearly balance the disadvantages in others for establishing a correct diagnosis and management, even when $^{123}$I-MIBG scintigraphy is restricted to patients who are at risk for metastatic disease. These results challenge some of the recommendation of Endocrine Society clinical practice PPGL guideline on the indications for $^{123}$I-MIBG scintigraphy. The role of $^{123}$I-MIBG scintigraphy could be mainly limited to metastatic PPGL when $^{131}$I-MIBG therapy is considered.

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Disclosure:
The authors declare that they have no conflict of interest.

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**Figure 1.** The three imaging scenarios are depicted for diagnoses based on CT/MRI, $^{123}$I-MIBG scintigraphy and CT/MRI combined with $^{123}$I-MIBG scintigraphy. Imaging-based diagnoses were based on imaging results were classified according to the following options: 1) no PPGL if no tumor was located; 2) unilateral; 3) extra-adrenal; 4) bilateral adrenal; 5) multi-focal; and, 6) metastatic. The virtual therapeutic modalities were classified using the following options: 1) unilateral adrenalectomy; 2) unifocal extra-adrenal tumor resection; 3) bilateral adrenalectomy; 4) multi-focal resection; and, 5) treatment of metastatic disease, respectively.

**Table 1.** Patient characteristics

| n=340 | n (%) |
|---|---|
| Age, years (mean, (range)) | 50 (19-84) |
| Sex | |
| female | 167 (49.1) |
| male | 173 (50.9) |
| Correct diagnosis | |
| Non-metastatic | 314 (92.4) |
| Metastatic | 26 (7.6) |
| Previous history of PPGL | 32 (9.4) |
| Biochemical phenotype | |
| Adrenergic | 182 (53.5) |
| Noradrenergic | 136 (40.0) |
| Dopaminergic | 1 (0.3) |
| none | 21 (6.2) |
| Hereditary syndrome | 102 (46.8)* |
| Primary tumor size > 6 centimeters | 75 (22.1) |

Abbreviations: PPGLs, pheochromocytomas and paragangliomas
* 19 SDHB, 14 SDHD, 9 VHL, 32 RET, 3 TMEM127, 3 MAX, 2 SDHA, 20 NF1

**Table 2.** Correct and imaging-based diagnoses

| | **Correct diagnoses (reference standard), n=340** | **Diagnoses based on CT/MRI only** | **Diagnoses based on $^{123}$I-MIBG only** | **Diagnoses based on CT/MRI plus $^{123}$I-MIBG** |
|---|---|---|---|---|
| Unilateral adrenal | 236 (69.4%) | 220 (64.7%) | 213 (62.6%) | 215 (63.2%) |
| Bilateral adrenal | 18 (5.3%) | 20 (5.9%) | 19 (5,6%) | 20 (5.9%) |
| Extra-adrenal (unifocal) | 48 (14.1%) | 42 (12.4%) | 44 (12.9%) | 39 (11.5%) |
| Multi-focal (adrenal/extra-adrenal) | 12 (3.5%) | 14 (4.1%) | 14 (4.1%) | 16 (4.7%) |
| Metastatic | 26 (7.6%) | 44 (12.9%) | 24 (7.1%) | 50 (14.7%) |
| No tumor | - | 0 (0%) | 26 (7.7%) | 0 (0%) |

**Table 3.** Rates of correct imaging-based diagnoses

| | **Diagnoses based on CT/MRI only** | **Diagnoses based on $^{123}$I-MIBG only** | **Diagnoses based on CT/MRI plus $^{123}$I-MIBG** |
|---|---|---|---|
| Correct diagnosis of non-metastatic PPGL (n=314) | 283 (90.1) | 279 (88.9) | 279 (88.9) |
| Correct diagnosis of unilateral adrenal PPGL (n=236) | 218 (92.4) | 210 (88.9) | 214 (90.7) |
| Correct diagnosis of bilateral adrenal PPGL (n=18) | 15 (83.3) | 16 (88.9) | 15 (83.3) |
| Correct diagnosis of extra-adrenal PPGL (n=48) | 39 (81.3) | 41 (85.4) | 38 (79.2) |
| Correct diagnosis of multifocal PPGL (n=12) | 11 (91.7) | 12 (100) | 12 (100) |
| Correct diagnosis of metastatic PPGL (n=26) | 21 (80.8) | 17 (65.4) | 23 (88.5) |

Abbreviations: PPGLs, pheochromocytomas and paragangliomas

**Table 4.** Impact of adding $^{123}$I-MIBG scintigraphy to CT/MRI on imaging-based diagnosis

| **Age** | **Gender** | **Recur-rence** | **Biochemical phenotype** | **Genotype** | **Tumor size >6cm** | **Correct diagnoses (reference standard), n=340** | **Diagnoses based on CT/MRI only** | **Diagnoses based on $^{123}$I-MIBG only** | **Diagnoses based on CT/MRI plus $^{123}$I-MIBG** | **Impact of adding $^{123}$I-MIBG on diagnosis** |
|---|---|---|---|---|---|---|---|---|---|---|
| 46 | M | + | NA | *SDHD* | - | Metastatic | Unilateral | Metastatic | Metastatic | Changed correctly |
| 58 | M | - | none | - | - | Metastatic | Extra- | Metastatic | Metastatic | Changed correctly |

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | adrenal | | | |
| 25 | M | - | NA | *SDHB* | - | Multi-focal | Extra-adrenal | Multi-focal | Multi-focal | Changed correctly |
| 64 | F | - | A | - | - | Unilateral | Bilateral | Unilateral | Unilateral | Changed correctly |
| | | | | | | | | | | |
| 57 | M | - | A | - | - | Unilateral | Unilateral | Bilateral | Bilateral | Changed incorrectly |
| | | | | | | | | | | |
| 24 | M | + | NA | *SDHA* | - | Extra-adrenal | Extra-adrenal | Bilateral | Multi-focal | Changed incorrectly |
| 24 | M | - | NA | - | - | Unilateral | Unilateral | Extra-adrenal | Multi-focal | Changed incorrectly |
| 75 | F | - | A | - | - | Unilateral | Unilateral | Metastatic | Metastatic | Changed incorrectly |
| 50 | F | - | none | - | - | Unilateral | Unilateral | Metastatic | Metastatic | Changed incorrectly |
| 40 | M | + | A | *RET* | - | Unilateral | Unilateral | Metastatic | Metastatic | Changed incorrectly |
| 49 | M | - | NA | - | - | Extra-adrenal | Multi-focal | Metastatic | Metastatic | Changed incorrectly |

Abbreviations: M, male; F, female; NA, noradrenergic A, adrenergic

**Table 5.** Virtual impact of adding $^{123}$I-MIBG scintigraphy to CT/MRI on patient management

| | **Based on CT/MRI only** | **Based on $^{123}$I -MIBG only** | **Based on CT/MRI plus $^{123}$I-MIBG** |
|---|---|---|---|
| Non-metastatic (n=314) | | | |
| appropriate surgery | 283 (90.1) | 279 (88.9) | 279 (88.9) |
| incomplete surgery | 1* (0.3) | 24 (7.6) | 0 (0) |
| redundant surgery | 7 (2.2) | 4 (1.3) | 8 (2.5) |
| surgery unjustly omitted | 23 (7.3) | 7 (2.2) | 27 (8.6) |
| Metastatic (n=26) | | | |
| appropriate treatment of metastatic disease | 21 (80.8) | 17 (65.4) | 23 (88.5) |
| redundant curative surgery | 5 (19.2) | 9 (34.6) | 3 (11.5) |

*chest lesion was missed because of abdominal CT only